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L7: Entry 10 of 10 File: USPT Apr 28, 1998

DOCUMENT-IDENTIFIER: US 5744446 A

**** See image for Certificate of Correction ****

TITLE: Hybrid human/animal factor VIII

Detailed Description Text (70):

Epitopes that are immunoreactive with antibodies that inhibit the coagulant activity of factor VIII ("inhibitors" or "inhibitory antibodies") have been characterized based on known structure-function relationships in factor VIII. Presumably, inhibitors could act by disrupting any of the macromolecular interactions associated with the domain structure of factor VIII or its associations with von Willebrand factor, thrombin, factor Xa, factor IXa, or factor X. However, over 90 percent of inhibitory antibodies to human factor VIII act by binding to epitopes located in the 40 kDa A2 domain or 20 kDa C2 domain of factor VIII, disrupting specific functions associated with these domains, as described by Fulcher et al., 82 Proc. Natl. Acad. Sci. USA 7728-7732 (1985), and Scandella et al., 85 Proc. Natl. Acad. Sci. USA 6152-6156 (1988). In addition to the A2 and C2 epitopes, there may be a third epitope in the A3 or C1 domain of the light chain of factor VIII, according to Scandella et al., 82 Blood 1767-1775 (1993). The significance of this putative third epitope is unknown, but it appears to account for a minor fraction of the epitope reactivity in factor VIII.

Detailed Description Text (78):

It is likely that clinically significant factor VIII epitopes are confined to the A2 and C2 domains. However, if antibodies to other regions (A1, A3, B, or C1 domains) of factor VIII are identified, the epitopes can be mapped and eliminated by using the approach described herein for the nonantigenic hybrid human/porcine factor VIII molecules.

Detailed Description Text (80):

For example, antibodies specific for the C1 or A3 domain epitope can be isolated from total patient IgG by affinity chromatography using the A1.sub.p -A2.sub.p -A3.sub.H -C1.sub.p -C2.sub.p and A1.sub.p -A2.sub.p -A3.sub.p -C1H-C2.sub.p hybrids, and by elimination of C2 specific antibodies by passage over recombinant factor VIII C2-Sepharose.TM.. The putative third epitope will be identified by SOE constructs in which, in a preferred embodiment, portions of the human factor VIII A3 or C1 domain are systematically replaced with porcine sequence.

h e b b g e e e f c e fg e ge

L8 ANSWER 130 OF 130 PHAR COPYRIGHT 2004 PJB on STN
AN 20145 PHAR
DN 031424
CN anti-FVIII MAb 2E9
CN 2E9 MAb, ThromboGenics
CN MAb-LE2E9
STA Active

CO

Type	Company Name (Country)	Development Status
Originator	ThromboGenics (Ireland)	Preclinical

SO Pharmaprojects. PJB Publications Ltd., Richmond, Surrey, UK
TX **Anti-FVIII** MAb 2E9 is a human type II **anti-Factor VIII** monoclonal **antibody** to the **C1** domain of **Factor VIII**, under development by ThromboGenics as an iv anticoagulant (Scrip Daily Online, 22 Jul 2003, S00809620).PreclinicalAnti-**FVIII** MAb 2E9 inhibited the binding of thrombin-activated **Factor VIII** to phosphatidylserine, with a plateau effect of 85% even when in excess (100x the IC50) (Company Web Page, ThromboGenics, 30 Oct 2000 and 13 Aug 2002).LicensingIt is available for licensing (Direct communication, ThromboGenics, 1 Mar 2001). Updated by KK on 23/7/2003.

L8 ANSWER 129 OF 130 GENBANK® COPYRIGHT 2004 on STN

LOCUS (LOC): AF234247 GenBank (R)
GenBank ACC. NO. (GBN): AF234247
GenBank VERSION (VER): AF234247.1 GI:13171321
CAS REGISTRY NO. (RN): 325613-50-1
SEQUENCE LENGTH (SQL): 361
MOLECULE TYPE (CI): mRNA; linear
DIVISION CODE (CI): Primates
DATE (DATE): 16 Aug 2001
DEFINITION (DEF): Homo sapiens clone KM33 immunoglobulin heavy chain variable region mRNA, partial cds.

SOURCE: human.
ORGANISM (ORGN): Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo
NUCLEIC ACID COUNT (NA): 83 a 85 c 113 g 80 t
REFERENCE: 1 (bases 1 to 361)
AUTHOR (AU): van den Brink,E.N.; Turenhout,E.A.; Bovenschen,N.; Heijnen,B.G.; Mertens,K.; Peters,M.; Voorberg,J.
TITLE (TI): Multiple VH genes are used to assemble human **antibodies** directed toward the A3-**C1** domains of **factor VIII**
JOURNAL (SO): Blood, 97 (4), 966-972 (2001)
OTHER SOURCE (OS): CA 134:294384
REFERENCE: 2 (bases 1 to 361)
AUTHOR (AU): van den Brink,E.N.; Voorberg,J.
TITLE (TI): Direct Submission
JOURNAL (SO): Submitted (15-FEB-2000) Plasma Proteins, CLB, Sanquin Blood Supply Foundation, Plesmanlaan 125, Amsterdam 1066 CX, The Netherlands

L4 ANSWER 13 OF 15 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 96:316787 SCISEARCH
THE GENUINE ARTICLE: UF406
TITLE: CLONING AND SEQUENCE-ANALYSIS OF HUMAN BREAST EPITHELIAL ANTIGEN BA46 REVEALS AN RGD CELL-ADHESION SEQUENCE PRESENTED ON AN EPIDERMAL GROWTH FACTOR-LIKE DOMAIN
AUTHOR: COUTO J R; TAYLOR M R; GODWIN S G; CERIANI R L; PETERSON J A (Reprint)
CORPORATE SOURCE: CANC RES FUND CONTRA COSTA, 2055 N BROADWAY, WALNUT CREEK, CA, 94596 (Reprint); CANC RES FUND CONTRA COSTA, WALNUT CREEK, CA, 94596
COUNTRY OF AUTHOR: USA
SOURCE: DNA AND CELL BIOLOGY, (APR 1996) Vol. 15, No. 4, pp. 281-286.
ISSN: 1044-5498.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 37

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The BA46 antigen of the human milk fat globule (HMFG) membrane is expressed in human breast carcinomas and has been used successfully as a target for experimental breast cancer radioimmunotherapy. To characterize this antigen further, we obtained the entire cDNA sequence and focused on its possible role in cell adhesion. The derived protein sequence of BA46 encodes a 387-residue precursor composed of a putative signal peptide, an amino-terminal epidermal growth factor (EGF)-like domain containing the cell adhesion tripeptide arginine-glycine-aspartic acid (RGD), and human factor V and **factor VIII** C1/C2-like domains.
The EGF-like domain of BA46 is similar to the calcium-binding EGF-like domains of several coagulation factors, but the BA46 domain lacks a residue required for calcium binding and the coagulation factor domains do not include an RGD sequence. Assuming that all EGF-like domains fold into a similar structure, the RGD-containing sequence in BA46 is inserted between two antiparallel beta strands, This positioning suggests a novel function for the EGF-like domain as a scaffold for RGD presentation.

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L7: Entry 5 of 10 File: USPT Oct 1, 2002

DOCUMENT-IDENTIFIER: US 6458563 B1
**** See image for Certificate of Correction ****
TITLE: Modified factor VIII

Detailed Description Text (31):
Epitopes that are immunoreactive with antibodies that inhibit the coagulant activity of factor VIII ("inhibitors" or "inhibitory antibodies") have been characterized based on known structure-function relationships in factor VIII. Presumably, inhibitors could act by disrupting any of the macromolecular interactions associated with the domain structure of factor VIII or its associations with von Willebrand factor, thrombin, factor Xa, factor IXa, or factor X. However, most inhibitory antibodies to human factor VIII act by binding to epitopes located in the 40 kDa A2 domain or 20 kDa C2 domain of factor VIII, disrupting specific functions associated with these domains, as described by Fulcher et al. (1985) Proc. Natl. Acad. Sci USA 82:7728-7732; and Scandella et al. (1988) Proc. Natl. Acad. Sci. USA 85:6152-6156. In addition to the A2 and C2 epitopes, there may be a third epitope in the A3 or C1 domain of the light chain of factor VIII, according to Scandella et al. (1993) Blood 82:1767-1775. The significance of this putative third epitope is unknown, but it appears to account for a minor fraction of the epitope reactivity in factor VIII.

Detailed Description Text (136):
Porcine fVIII is typically less reactive with inhibitory antibodies that arise in hemophiliacs who have been transfused with fVIII or which arise as autoantibodies in the general population. This is the basis for using porcine fVIII concentrate in the management of patients with inhibitory antibodies [Hay and Lozier (1995) supra]. Most inhibitors are directed against epitopes located in the A2 domain or C2 domain [Fulcher, C. A. et al. (1985) Proc. Natl. Acad. Sci. USA 82:7728-7732; Scandella, D. et al. (1988) Proc. Natl. Acad. Sci. USA 85:6152-6156; Scandella, D. et al. (1989) Blood 74:1618-1626]. Additionally, an epitope of unknown significance has been identified that is in either the A3 or C1 domain [Scandella et al. (1989) supra; Scandella, D. et al. (1993) Blood 82:1767-1775; Nakai, H. et al. (1994) Blood 84:224a]. The A2 epitope has been mapped to residues 484-508 by homolog scanning mutagenesis [Healey et al. (1995) supra]. In this 25 residue segment, there is relatively low proportion of identical sequence (16/25 or 64%). It is interesting that this region, which appears to be functionally important based on the fact that antibodies to it are inhibitory, apparently has been subjected to relatively more rapid genetic drift. Alignment of the porcine A2 domain and A3 domains indicate that the A2 epitope shares no detectable homology with the corresponding region in the A3 domain.

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L7: Entry 6 of 10 File: USPT Apr 23, 2002

DOCUMENT-IDENTIFIER: US 6376463 B1
** See image for Certificate of Correction **
TITLE: Modified factor VIII

Detailed Description Text (70):
Epitopes that are immunoreactive with antibodies that inhibit the coagulant activity of factor VIII ("inhibitors" or "inhibitory antibodies") have been characterized based on known structure-function relationships in factor VIII. Presumably, inhibitors could act by disrupting any of the macromolecular interactions associated with the domain structure of factor VIII or its associations with von Willebrand factor, thrombin, factor Xa, factor IXa, or factor X. However, over 90% of inhibitory antibodies to human factor VIII act by binding to epitopes located in the 40 kDa A2 domain or 20 kDa C2 domain of factor VIII, disrupting specific functions associated with these domains, as described by Fulcher et al. (1985) Proc. Natl. Acad. Sci USA 82:7728-7732; and Scandella et al. (1988) Proc. Natl. Acad. Sci. USA 85:6152-6156. In addition to the A2 and C2 epitopes, there may be a third epitope in the A3 or C1 domain of the light chain of factor VIII, according to Scandella et al. (1993) Blood 82:1767-1775. The significance of this putative third epitope is unknown, but it appears to account for a minor fraction of the epitope reactivity in factor VIII.

Detailed Description Text (78):
It is likely that clinically significant factor VIII epitopes are confmed to the A2 and C2 domains. However, if antibodies to other regions (A1, A3, B, or C1 domains) of factor VIII are identified, the epitopes can be mapped and eliminated by using the approach described herein for the nonantigenic hybrid human/porcine factor VIII molecules.

Detailed Description Text (80):
For example, antibodies specific for the C 1 or A3 domain epitope can be isolated from total patient IgG by affinity chromatography using the A1.sub.p -A2.sub.p -A3.sub.H -C1.sub.p -C2.sub.P and A1.sub.p -A2.sub.p -A3.sub.p -C1.sub.H -C2.sub.P hybrids, and by elimination of C2 specific antibodies by passage over recombinant factor VIII C2-Sepharaose.TM.. The putative third epitope will be identified by SOE constructs in which, in a preferred embodiment, portions of the human factor VIII A3 or C1 domain are systematically replaced with porcine sequence.

Detailed Description Text (274):
Porcine fVIII is typically less reactive with inhibitory antibodies that arise in hemophiliacs who have been transfused with fVIII or which arise as autoantibodies in the general population. This is the basis for using porcine fVIII concentrate in the management of patients with inhibitory antibodies [Hay and Lozier (1995) supra]. Most inhibitors are directed against epitopes located in the A2 domain or C2 domain [Fulcher, C. A. et al. (1985) Proc. Natl. Acad. Sci. USA 82:7728-7732; Scandella, D. et al. (1988) Proc. Natl. Acad. Sci. USA 85:6152-6156; Scandella, D. et al. (1989) Blood 74:1618-1626]. Additionally, an epitope of unknown significance has been identified that is in either the A3 or C1 domain [Scandella et al. (1989) supra; Scandella, D. et al. (1993) Blood 82:1767-1775; Nakai, H. et al. (1994) Blood 84:224a]. The A2 epitope has been mapped to residues 484-508 by homolog scanning mutagenesis [Healey et al. (1995) supra]. In this 25 residue segment,

there is relatively low proportion of identical sequence (16/25 or 64%). It is interesting that this region, which appears to be functionally important based on the fact that antibodies to it are inhibitory, apparently has been subjected to relatively more rapid genetic drift. Alignment of the porcine A2 domain and A3 domains indicate that the A2 epitope shares no detectable homology with the corresponding region in the A3 domain.

h e b b g e e e f c e fg e ge

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L7: Entry 7 of 10 File: USPT Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6180371 B1
** See image for Certificate of Correction **
TITLE: Modified factor VIII

Detailed Description Text (69):
Epitopes that are immunoreactive with antibodies that inhibit the coagulant activity of factor VIII ("inhibitors" or "inhibitory antibodies") have been characterized based on known structure-function relationships in factor VIII. Presumably, inhibitors could act by disrupting any of the macromolecular interactions associated with the domain structure of factor VIII or its associations with von Willebrand factor, thrombin, factor Xa, factor IXa, or factor X. However, over 90 percent of inhibitory antibodies to human factor VIII act by binding to epitopes located in the 40 kDa A2 domain or 20 kDa C2 domain of factor VIII, disrupting specific functions associated with these domains, as described by Fulcher et al. (1985) Proc. Natl. Acad. Sci USA 82:7728-7732; and Scandella et al. (1988) Proc. Natl. Acad. Sci. USA 85:6152-6156. In addition to the A2 and C2 epitopes, there may be a third epitope in the A3 or C1 domain of the light chain of factor VIII, according to Scandella et al. (1993) Blood 82:1767-1775. The significance of this putative third epitope is unknown, but it appears to account for a minor fraction of the epitope reactivity in factor VIII.

Detailed Description Text (79):
For example, antibodies specific for the C1 or A3 domain epitope can be isolated from total patient IgG by affinity chromatography using the A1.sub.p - A2.sub.p - A3.sub.H -C1.sub.p -C2.sub.p and A1.sub.p -A2.sub.p -A3.sub.p -C1.sub.H -C2.sub.p hybrids, and by elimination of C2 specific antibodies by passage over recombinant factor VIII C2-Sepharaose.TM.. The putative third epitope will be identified by SOE constructs in which, in a preferred embodiment, portions of the human factor VIII A3 or C1 domain are systematically replaced with porcine sequence.

Detailed Description Text (266):
Porcine fVIII is typically less reactive with inhibitory antibodies that arise in hemophiliacs who have been transfused with fVIII or which arise as autoantibodies in the general population. This is the basis for using porcine fVIII concentrate in the management of patients with inhibitory antibodies [Hay and Lozier (1995) supra]. Most inhibitors are directed against epitopes located in the A2 domain or C2 domain [Fulcher, C. A. et al. (1985) Proc. Natl. Acad. Sci. USA 82:7728-7732; Scandella, D. et al. (1988) Proc. Natl. Acad. Sci. USA 85:6152-6156; Scandella, D. et al. (1989) Blood 74:1618-1626]. Additionally, an epitope of unknown significance has been identified that is in either the A3 or C1 domain [Scandella et al. (1989) supra; Scandella, D. et al. (1993) Blood 82:1767-1775; Nakai, H. et al. (1994) Blood 84:224a]. The A2 epitope has been mapped to residues 484-508 by homolog scanning mutagenesis [Healey et al. (1995) supra]. In this 25 residue segment, there is relatively low proportion of identical sequence (16/25 or 64%). It is interesting that this region, which appears to be functionally important based on the fact that antibodies to it are inhibitory, apparently has been subjected to relatively more rapid genetic drift. Alignment of the porcine A2 domain and A3 domains indicate that the A2 epitope shares no detectable homology with the corresponding region in the A3 domain.

L4 ANSWER 12 OF 15 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:113859 BIOSIS
DOCUMENT NUMBER: PREV199900113859
TITLE: The Arg 2150 His mutation within the **factor VIII C1** domain eliminates a B cell epitope that is present only on **factor VIII**-von Willebrand factor complexes.
AUTHOR(S): Gilles, J. G. G.; Lavend'homme, R.; Peerlinck, K.; Jacquemin, M.; Hoylaerts, M.; Jorieux, S.; Mazurier, C.; Vermylen, J.; Saint-Remy, J.-M.
CORPORATE SOURCE: Cent. Molecular Vascular Biology, Univ. Leuven, Leuven, Belgium
SOURCE: Blood, (Nov. 15, 1998) Vol. 92, No. 10 SUPPL. 1 PART 1-2, pp. 710A. print.
Meeting Info.: 40th Annual Meeting of the American Society of Hematology. Miami Beach, Florida, USA. December 4-8, 1998. The American Society of Heamatology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Mar 1999
Last Updated on STN: 12 Mar 1999

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5859204		19990112
APPLICATION INFO.:	US 1996-670707		19960626 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-212133, filed on 11 Mar 1994, now patented, Pat. No. US 5663060 which is a continuation-in-part of Ser. No. US 1992-864004, filed on 7 Apr 1992, now patented, Pat. No. US 5364771

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wax, Robert A.
ASSISTANT EXAMINER: Longton, Enrique D.
LEGAL REPRESENTATIVE: Greenlee Winner and Sullivan
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT: 4479
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Site-specific replacement of amino acids in the region of positions 484-509 of human factor VIII can result in reduction of reactivity to an inhibitory **antibody** while procoagulant activity is retained. Modified human factor VIII having an immunoreactivity-reducing amino acid substituted for the naturally occurring amino acid is described.

L15 ANSWER 47 OF 69 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1998-077108 [07] WPIDS
CROSS REFERENCE: 1993-336824 [42]; 1995-328236 [42]; 1998-271107 [24]; 1999-551355 [46]; 2001-016350 [02]; 2001-596886 [67]
DOC. NO. CPI: C1998-025821
TITLE: New modified factor VIII molecules - having reducing immunogenicity.
DERWENT CLASS: B04 D16
INVENTOR(S): LOLLAR, J S
PATENT ASSIGNEE(S): (UYEM-N) UNIV EMORY; (LOLL-I) LOLLAR J S
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9749725	A1	19971231	(199807)*	EN	125
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP US					
AU 9736433	A	19980114	(199822)		
US 5859204	A	19990112	(199910)		
EP 939767	A1	19990908	(199941)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
AU 717686	B	20000330	(200026)		
JP 2000513934	W	20001024	(200058)		156
US 2003068785	A1	20030410	(200327)		
CA 2258502	C	20030429	(200337)	EN	

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9749725	A1		WO 1997-US11155	19970626
AU 9736433	A		AU 1997-36433	19970626
US 5859204	A	CIP of	US 1992-864004	19920407
		CIP of	US 1994-212133	19940311
		CIP of	WO 1994-US13200	19941115
			US 1996-670707	19960626
EP 939767	A1		EP 1997-933180	19970626
			WO 1997-US11155	19970626
AU 717686	B		AU 1997-36433	19970626
JP 2000513934	W		WO 1997-US11155	19970626
			JP 1998-503544	19970626
US 2003068785	A1	CIP of	US 1996-670707	19960626
		CIP of	US 1998-37601	19980310
		Div ex	US 2000-523656	20000310
			US 2002-187319	20020628
CA 2258502	C		CA 1997-2258502	19970626
			WO 1997-US11155	19970626

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9736433	A	Based on	WO 9749725
US 5859204	A	CIP of	US 5364771
		CIP of	US 5663060
EP 939767	A1	Based on	WO 9749725
AU 717686	B	Previous Publ.	AU 9736433
		Based on	WO 9749725
JP 2000513934	W	Based on	WO 9749725
US 2003068785	A1	CIP of	US 5859204
		CIP of	US 6180371
		Div ex	US 6458563

CA 2258502 C Based on WO 9749725

PRIORITY APPLN. INFO: US 1996-670707 19960626; US
1992-864004 19920407; US
1994-212133 19940311; WO
1994-US13200 19941115

AB WO 9749725 A UPAB: 20030612

(A) Modified **factor VIII** is claimed consisting of an amino acid substitution at one or more of positions 484, 485, 487, 488, 489, 492, 495, 501, 508 or 2181-2243, as in a 2332 amino acid sequence (given in the specification), the substitution being insertion of an immunoreactivity-reducing amino acid for the naturally-occurring amino acid, the modified **factor VIII** having procoagulant activity. Also claimed are: (B) isolated and purified DNA comprising a nucleotide sequence encoding an amino acid sequence of porcine **factor VIII**; (C) isolated and purified DNA comprising a nucleotide sequence encoding an A1 domain of porcine **factor VIII** from amino acids 20 to 391; (D) isolated and purified DNA comprising a nucleotide sequence encoding a A3 domain of porcine **factor VIII** from amino acids 801 to 1130; (E) isolated and purified DNA comprising a nucleotide sequence encoding a **C1 domain** of porcine **factor VIII** from amino acids 1131 to 1283; (F) isolated and purified DNA comprising a nucleotide sequence encoding a C2 domain of porcine **factor VIII** from amino acids 1284 to 1433; and (G) hybrid human/non-human mammalian **factor VIII** comprising a segment of a non-human **factor VIII** that corresponds to a segment of amino acids 2181 to 2243 of the 2332 amino acid sequence.

USE - The factor VIII molecules have coagulant activity and can be used for treating factor VIII deficiency, particularly for treating patients with haemophilia. The products can also be used in detection and diagnosis.

ADVANTAGE - The modified factor VIII has less immunoreactivity with naturally occurring inhibitory antibodies to factor VIII and/or is less apt to elicit the production of antibodies to factor VIII than human factor VIII. Some of the hybrid factor VIII molecules have specific activity greater than that of human factor VIII and equal to or greater than that of porcine factor VIII.

L15 ANSWER 30 OF 69 USPATFULL on STN

ACCESSION NUMBER:	1999:40394 USPATFULL
TITLE:	Hybrid human/animal factor VIII
INVENTOR(S):	Lollar, John S., Decatur, GA, United States Runge, Marschall S., Galveston, TX, United States
PATENT ASSIGNEE(S):	Emory University, Atlanta, GA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5888974		19990330
APPLICATION INFO.:	US 1995-475201		19950607 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-212133, filed on 11 Mar 1994, now patented, Pat. No. US 5663060 which is a continuation-in-part of Ser. No. US 1992-864004, filed on 7 Apr 1992, now patented, Pat. No. US 5364771

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Jacobson, Dian C.
LEGAL REPRESENTATIVE:	Greenlee Winner and Sullivan PC
NUMBER OF CLAIMS:	2
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT:	3281

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A hybrid procoagulant factor VIII is produced by isolation and recombination of human and other nonhuman mammalian factor VIII subunits or domains, or by genetic engineering of the human and animal factor VIII genes. Subunits or domains of factor VIII that have been purified from human or animal plasma are isolated, and hybrid human/animal factor VIII is produced by (1) mixing either animal heavy chain subunits with human light chain subunits or by mixing human heavy chain subunits with animal light chain subunits, thereby producing human light chain/animal heavy chain and human heavy chain/animal light chain hybrid molecules; or by (2) mixing one or more domains of one species with one or more domains of the other species. These hybrid molecules are isolated by ion exchange chromatography. Alternatively, recombinant DNA methods are used to change elements of animal factor VIII or human factor VIII to the corresponding elements of human factor VIII or animal factor VIII, respectively, to produce hybrid human/animal factor VIII. A recombinant hybrid equivalent factor VIII molecule is produced by substituting amino acid sequence having no known factor VIII sequence identity for specific amino acid sequence in the human or animal factor VIII. The hybrid factor VIII and hybrid equivalent factor VIII molecules are administered to patients having factor VIII deficiency.